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HADDAD, MAHER M	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 04/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/763,424	KARLIK ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-59* is/are pending in the application.

4a) Of the above claim(s) *25-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24 and 46-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-59 are pending.

2. Applicant's election with traverse of Group I, claims 1-24 and 46-59 drawn to a method of promoting remyelination of nerve cells or reversing paralysis in a mammal comprising administering a remyelinating agent, filed on 2/27/06, is acknowledged.

Applicant's traversal is on the grounds that any nominal burden placed upon the Examiner to search accordingly to determine the art relevant to applicants' overall invention is significantly out weighted by the public's interest in not having to obtain and study many separate patents in order to have available all of the issued patent claims covering Applicants' invention. Applicant submits that the process would place an unnecessary burden on both PTO and the Applicants. Citing MPEP 803, Applicant submits that regardless of whether the five inventions are independent or distinct, the Examiner need not have restricted the application. This is not found persuasive because various remyelinating agents and combination thereof differ with respect to their structures and physicochemical properties; therefore each product is patentably distinct. Further, a prior art search also requires a literature search. It is an undue burden for the examiner to search more than one invention.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 25-45 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 1-24 and 46-59 are under examination as they read on a method of promoting remyelination of nerve cells or reversing paralysis in a mammal comprising administering a remyelinating agent.

5. Claim 13 is objected to under 37 CFR § 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim (i.e., claim 5).

6. Claims 12 and 14 are objected to because they depend on "claim ii", it appears that claims 12 and 14 should depend from claim 11. Correction is required.

7. Claim 16 is objected to for the following informalities: "1 gnome" is misspelled. Correction is required.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 11-16 and 55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 11-16 and 55 are indefinite in that they only describe the compositions of interest by an arbitrary protein name, "natalizumab". Claiming biochemical molecules by a particular name given to the protein by various workers in the field fails to distinctly claim what that antibody is and what compositions comprising that antibody are made.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 11-16 and 55 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the hybridoma that produce the starting material for natalizumab antibody, MAB 21.6, is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, a deposit of the hybridoma or the host cell, which produces this antibody, may satisfy first paragraph. See 37 CFR 1.801-1.809.

If the deposit has been made under the terms of the Budapest Treaty, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the hybridoma has been deposited under the Budapest Treaty and that the hybridoma will be irrevocably and without restriction or condition released to the public upon the issuance of a patent would satisfy the deposit requirement made herein. See 37 CFR 1.808. If the deposit has not been made under the Budapest treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth in 37 CFR 1.801-1.809, have been met.

If the deposit was made after the effective filing date of the application for a patent in the United States, a verified statement is required from a person in a position to corroborate that the hybridoma described in the specification as filed are the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Further, amendment of the specification to disclose the date of deposit and the complete name and address of the depository (ATCC.10801 University Boulevard, Manassas, VA 20110-2209) is required as set forth in 37 C.F.R. 1.809(d).

12. Claims 1-24 and 46-59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of promoting remyelination of nerve cells or reversing paralysis in a multiple sclerosis subject comprising administering to the mammal in need thereof anti-VLA-4 antibody does not reasonably provide **enablement** for a method of promoting "remelination of nerve cells in a mammal" comprising administering to the mammal in need thereof any "remyelinating agent" in a remyelinating effective amount in claim 1, wherein the mammal is a human in claim 2, wherein the human suffers from the conditions recited in claim 3, wherein the human suffers from multiple sclerosis in claim 4, wherein the agent is any "antibody or an immunological active fragment thereof" in claim 5, wherein the antibody is any "monoclonal antibody or an immunologically active fragment of any monoclonal antibody" in claim 6, wherein the monoclonal antibody is any "chimeric antibody, any human antibody" any genetically engineered antibody or any bispecific antibody" in claim 7, wherein the chimeric antibody is any humanized or primatized in claim 8, wherein the antibody or an immunologically active fragment thereof that binds to alpha-4beta-1 integrin in claim 9, wherein the antibody is a humanized antibody or an immunologicallly active fragment thereof in claim 10, wherein the humanized antibody is natalizumab or an immunologically active fragment thereof in claim 11, wherein natalizumab is administered intravenously or subcutaneously in claim 12, wherein the immunologically active fragment of the antibody is Fab, scFv or F(ab`)2 in claim 13, wherein the natalizumbis administered chronically to the mammal in need in claim 14, wherein natalizumab/remyelinating agent as recited in claim 15-24, or a method of reversing paralysis in a subject with a demyelination disease comprising administerting to to the subject a "remyelinating agent" in lcaim 46, wherein the subject with paralysis suffers for conditions recited in claim 47. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

Applicant has not provided sufficient biochemical information that distinctly identifies such "remyelinating agent", "antibody", "monoclonal antibody", "chimeric antibody". While any

remyelinating agent may have some notion of the activity of the "promoting agent", claiming biochemical molecules by such properties fails to provide sufficient guidance and direction as to how the skilled artisan can make such agents, commensurate in scope with the claimed invention. The specification fails to provide any guidance on how to make such agents that can be used to promote remyelination of nerve cells or reverse paralysis.

Further the specification under Example 2, discloses that the model of immune cell influx into the central nervous system being blocked by inhibiting alpha-4 beta-1 ($\alpha4\beta1$) integrin (VLA-4) blocks was studied to determine whether the presence of inflammatory cells suppresses spontaneous myelin repair in experimental autoimmune encephalomyelitis. Paralyzed guinea pigs were treated in an advanced, demyelinated stage of EAE with the $\alpha4\beta1$ specific inhibitor, N-[N-(3-pyridinesulfonyl)-L-3,3-dimethyl-4-thiaprolyl-]-O-[1-methylpiperazin-4-ylcarbonyl]-L-tyrosine isopropyl ester (Piraino et al., J. Neuroimmunol. 2002, 131:147-159), and we found that: (1) 87% of plaques showed evidence of remyelination after 40 days of treatment; (2) myelin repair occurred in 50% of the total lesion area; and (3) 50% of the animals regained motor function. There was no significant repair or gain of motor function in vehicle treated animals. These results indicate that prolonged inhibition of CNS inflammation, in the absence of targeted myelin repair, can facilitate mechanisms of spontaneous remyelination (example 2).

In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Besides the EAE animal model for MS, no animal model system is used to promote remyelination of nerve cells or reversing paralysis in a congenital metabolic disorder, a neurophathy with abnormal myelination, drug induced demyelination, radiation induced demyelination a heraeditary demyelinating condition, a prion induced demyelination condition, encephalitis induced demyelination or a spinal cord injury. Since the method of promoting and reversing indices of administering to the animal an anti-VLA-4 antibody can be species- and model-dependent, it is not clear that reliance on the EAE studies accurately reflects the relative human efficacy of the claimed therapeutic strategy. Besides MS, the specification does not adequately teach how to effectively promote remyeliantion of nerve or reach any therapeutic endpoint in humans by administering the anti-VLA-4 antibodies. The specification does not teach how to extrapolate data obtained from in EAE studies to the development of effective in vivo mammalian including human therapeutic treatment, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the anti-VLA-4 antibodies exemplified in the specification. While novel drugs for preventing demyelination are needed for treating clinical disorders involving the demyelinating diseases of peripheral nerve. Currently, there is no effective therapy available for hereditary motor and sensory demyelinating neuropathies (e.g., HMSN Type I) and no effective treatment for Guillain-Barre syndrome (as an example).

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

13. Claims 1-24 and 46-5are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of a method of promoting remyelination of nerve cells or reversing paralysis in a multiple sclerosis subject comprising administering to the mammal in need thereof anti-VLA-4 antibody.

Applicant is not in possession of a method of promoting "remelination of nerve cells in a mammal" comprising administering to the mammal in need thereof any "remyelinating agent" in a remyelinating effective amount in claim 1, wherein the mammal is a human in claim 2, wherein the human suffers from the conditions recited in claim 3, wherein the human suffers from multiple sclerosis in claim 4, wherein the agent is any "antibody or an immunological active fragment thereof" in claim 5, wherein the antibody is any "monoclonal antibody or an immunologically active fragment of any monoclonal antibody" in claim 6, wherein the monoclonal antibody is any "chimeric antibody, any human antibody" any genetically engineered antibody or any bispecific antibody" in claim 7, wherein the chimeric antibody is any humanized or primatized in claim 8, wherein the antibody or an immunologically active fragment thereof that binds to alpha-4beta-1 integrin in claim 9, wherein the antibody is a humanized antibody or an immunologicallly active fragment thereof in claim 10, wherein the humanized antibody is natalizumab or an immunologically active fragment thereof in claim 11, wherein natalizumab is administered intravenously or subcutaneously in claim 12, wherein the immunologically active fragment of the antibody is Fab, scFv or F(ab`)2 in claim 13, wherein the natalizumbis administered chronically to the mammal in need in claim 14, wherein natalizumab/remyelinating agent as recited in claim 15-24, or a method of reversing paralysis in a subject with a demyelination disease comprising administerting to to the subject a "remyelinating agent" in lcaim 46, wherein the subject with paralysis suffers for conditions recited in claim 47.

Applicant has disclosed only anti-VLA-4 antibody in treating MS; therefore, the skilled artisan cannot envision all the contemplated agents possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show

the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol: 66, No. 4, pages 1099-1111, Friday January 5, 2001.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 1-4 and 46-48 are rejected under 35 U.S.C. 102(b) as being anticipated by Cannella et al (proc. Natl. Acad. Sci USA. 95:10100-10105, 1998).

Cannella et al teach a method of promoting remyelination of nerve cells in a mammal (MS patient) comprising administering to the mammal in need thereof a remylinating agent (glial growth factor 2), rhGGF2)) (see abstract and page 10105 last paragraph in particular).

While the reference is silence with regard to "reversing paralysis" per se; the method, the product used in the reference method are the same as the claimed method. Therefore this limitation is considered inherent properties.

The reference teachings anticipate the claimed invention.

16. Claims 1-8 and 46-48 are rejected under 35 U.S.C. 102(b) as being anticipated by Warrington et al (PNAS. 97:6820-6825, 2000).

Warrington et al teach a method of promoting remyelination of nerve cells in a mammal (MS patient) comprising administering to the mammal in need thereof a human monoclonal antibody reactive to oligodendrocytes (a remylinating agent) (see abstract and page 6825 last paragraph in

particular). Warrington et al teach that human mAbs can be produced free for poteintial pathogen infection and can be structurally altered to augment their effectiveness and immunogenicity . In contrast to mouse mAbs or "humanized" mouse mAbs, human mAbs shold result inminimal immune response and are readily applicable to human trials. Further, Given that human mAbs promoted remyelination in chronically paralyzed animals provides hope that successful therapies can be developed for patients with long standing disabilities (see last paragraph in particular).

The reference teachings anticipate the claimed invention.

17. Claims 1-17, 19-20, 24, 46-55, 57 and 58 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 0015247.

The `247 publication teaches a method of treating multiple myeloma (MM) comprising administering to an individual (human) an antibody that antagonizes the interaction of VLA-4 (alpha-4 beta1) integrin with its ligand (see published claims 1-3 in particular). The `247 publication further teaches the antibody is selected from the group consisting of a human antibody, a chimeric antibody, a humanized antibody and fragments thereof (see published claim 5 in particular). The `247 publication also teaches that the several mouse anti-VLA-4 monoclonal antibodies are capable of recognizing the a chain of VLA-4 will be useful in the methods of treatment (see page 19, lines 5-10 in particular). Furthermore, the `247 publication teaches humanized anti-VLA4 antibodies comprise three complementarity determining regions (CDR1-3) having amino acid sequences from the corresponding CDRs of a mouse 21.6 immunoglobulin light/heavy chain and a variable region framework from a human kappa light chain variable region framework sequence except in at least position the amino acid position is occupied by the same amino acid present in the equivalent position of the mouse 21.6 immunoglobulin light/heavy chain variable region framework (i.e., natalizumab) (see page 23, lines 11-26 in particular). The `247 publication teaches that the anti-VLA-4 antibody are preferably administered parentally including intravenous and subcutaneous (see page 23, lines 30-34 in particular). In addition the `247 publication teaches that the antibody includes Fab fragments, $F(ab')_2$ fragment. Also, the `247 publication teaches the compositions also comprise and additional agent such as antiinflammatories, immunosuppressants, interferons and sulfasalazine(see page 26, lines 9-20 in particular).

Claims 14 and 17 are included because the `247 publication teaches that the antibodies will be administered at intervals of every 1-14 days (biweekly) as defined by the specification on page 32, lines 3-10 that the chronic administration is preferably biweekly, weekly, monthly or every other month but can be daily.

Claims 15 and 16 are included because while the reference does not measure the blood level of natalizumab in the individual, however, the specification provides the same dose of administration (i.e., 1-5mg/kg body weight/day (see page 253, lines 19-24)) fall within the same

range taught by `247 publication which .01-20mg/kg body weight/day. Therefore, the result of the intravenously administration of the antibody would result in blood level of natalizumab of at least about 1 ng/ml.

While the `247 publication is silence with regard to "remyelination of nerve cells" and "reversing paralysis" per se; the method, the product used in the reference method are the same as the claimed method. Therefore these limitations are considered inherent properties.

The reference teachings anticipate the claimed invention.

18. Claims 1-17, 46-48 and 50-55 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Pat. No.5,840,299.

The `299 patent teaches a method of treating central nervous system in patient (human) comprising administering to the patient a composition comprising humanized MAB 21.6 (i.e., anti-alpha4beta1 antibody, natalizumab) to block α4-dependent interactions of the VLA-4 receptor (see col., 14, under Methods of Treatment and claims 27-29 in particular). Furthermore, the `299 patent teaches a binding fragment of the humanized antibody. The fragments exhibit specific binding to the VLA-4 antigen, wherein humanized antibody fragments include separate heavy chains, light chains Fab, Fab', $F(ab')_2$, Fabc, and Fv (see col., 12, under Fragments of Humanized antibodies in particular). In addition, the `299 patent teaches that chimeric light and heavy chains were constructed for the mouse 21.6 $V_L$ and $V_H$ regions (see Example 2, col., 18in particular). The `299 patent also teaches the monoclonal antibody 21.6 (see col., 3, lines 36-39 in particular). The `299 patent teaches that the pharmaceutical compositions can be administered by intravenous or subcutaneous administration. (see col., 15, lines 59-65 in particular). Furthermore, the antibody is administered by intravenous infusion or subcutaneous injection at a dose from 1 to 5 mg antibody per kilo of bodyweight. The dose is repeated at interval from 2 to 8 weeks. Within this range, the preferred treatment regimen is 3 mg antibody per kilo of bodyweight repeated at a 4 week interval (see col., 16, lines 17-22 in particular).

Claims 14 and 17 are included because the `299 patent teaches that the interval from 2 to 8 weeks as defined by the specification on page 32, lines 3-10 that the chronic administration is preferably biweekly, weekly, monthly or every other month but can be daily.

Claims 15 and 16 are included because while the reference does not measure the blood level of natalizumab in the individual, however, the specification provides the same dose of administration (i.e., 1-5mg/kg body weight/day (see page 253, lines 19-24)) fall within the same range taught by `299 publication which 1-5mg/kg body weight/day (see col., 16, lines 17-22). Therefore, the result of the intravenously administration of the antibody would result in blood level of natalizumab of at least about 1 ng/ml.

While the `299 patent is silence with regard to "remyelination of nerve cells" and "reversing paralysis" per se; the method, the product used in the reference method are the same as the claimed method. Therefore these limitations are considered inherent properties.

The reference teachings anticipate the claimed invention.

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

20. Claims 1, 17-18, 46, 50, 51 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/15247 OR U.S. Pat. No. 5,840,299.

The teachings of `247 publication and the `299 patent have been discussed, supra.

The `247 publication further teaches that that the amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated, and the particular mode of administration. Further it should be under stood that the specific dosage and treatment regiment for any particular patient will depend upon a variety of factors and the judgment of the treating physician and the severity of the particular disease being treated. Also, the `247 publication teaches that the dosage and dose rate of the compounds effective to prevent, suppress or inhibit cell adhesion will depend on a variety of factors, such as the nature of the inhibitor, the size of the patient, the goal of the treatment, the nature of the pathology to be treated, the specific pharmaceutical composition used and the judgment of the treating physician (see page 26 lines 20-35 in particular).

The reference teachings does not explicitly teach the administration of remyelinating agent/anti-VLA-4 weekly or monthly for at least one year in claims 18 and 56.

It is clear that both the prior art and claimed method administer the same treatment to achieve the same results. It would be conventional and within the skill of the art to administer the remyelinating agent/anti-VLA-4 weekly or monthly for at least one year. The determination of the optimal intervals of treatment is well within the purview of one of ordinary skill in the art at the time the invention was made and lends no patentable import to the claimed invention. The duration of treatment, the specific rout of administration and like factors within the knowledge

and expertise of the medical practitioner. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

21. Claims 1-4, 19-21, 49, 57 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/15247 in view of U.S. Pat. No 6,284,473.

The teachings of the `247 publication have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation that the interferon is interferon bet-1b in claims 21 and 58.

The `473 patent teaches that recombinant interferon beta-1b (IFN.beta.-1b) is the first therapeutic agent which can alter the natural history of relapsing-remitting multiple sclerosis by reducing the number and severity of relapses and the volume of white matter detected by cranial MRI (see col., 1 lines 55-65 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the interferon taught by the `247 publication with interferon beta-1b taught by the `473 patent in a method of promoting remyelinating of nerve cell/reversing paralysis in MM subject.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because interferon beta-1b (IFNβ1b) is the first therapeutic agent which can alter the natural history of relapsing-remitting multiple sclerosis by reducing the number and severity of relapses and the volume of white matter detected by cranial MRI as taught by the `473 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

22. Claims 1-4, 19-20, 22-23, 49, 57 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/15247 or U.S. Pat. No. 5,840,299, each in view of U.S. Pat. No 6,753,135.

The teachings of the `247 publication and the `299 patent have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of that the corticosteroide is prednisone in claims 23 and 59.

The `135 patent teaches that prednisone is a corticosteroid used to treat a wide variety of inflammatory disorders, including multiple sclerosis. The `135 patent further teaches that the prednisone and other glucocorticoids are known to have broad-ranging anti-inflammatory and immunosuppressive effects, including inhibition of pro-inflammatory mediators and activation of anti-inflammatory mediators. They affect the growth, differentiation, and function of monocytes and lymphocytes; the distribution of cellular subsets; and the production of cytokines, cellular proteins that are secreted and affect the behavior of other cells. (see col., 1 lines 30-45 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to co-administer prednisone taught by the `135 patent with anti-VLA-4 antibodies taught by the `247 publication/`299 patent in a method of promoting remyelinating of nerve cell/reversing paralysis in MM subject.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because prednisone is used to treat a wide variety of inflammatory disorders, including multiple sclerosis as taught by the `135 patent. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205USPQ 1069, 1072 (CCPA 1980) (see MPEP 2144.06).

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

23. Claims 1-4, 19-21, 57 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Pat. No. 5,840,299 in view of U.S. Pat. No. 6,602,885.

The teachings of the `299 patent have been discussed, supra.

The claimed invention differs from the `299 patent teachings only by the recitation of a combination therapy comprising an anti-inflammatory agent in claim 19, wherein said agent is interferon in claims 20 and 57, wherein the interferon is interferon beta-1b in claims 21 and 58..

The `885 patent teaches agents known in the treatment of inflammatory bowel disease and multiple sclerosis which can be administered in combination with the CCR5 antagonists are as

follows: multiple sclerosis: interferon-beta, interferon-alpha, and steroids.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine interferon beta-1b or interferon beta-a with the natalizumab in a in the method of treatment of MM as taught by the '299 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to combine said compound with the natalizumab because agents known in the treatment of multiple sclerosis can be administered in combination, presumably to the ameliorates the pathological inflammation, and the combination of compound that ameliorates the pathological inflammation would be considered obvious. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205USPQ 1069, 1072 (CCPA 1980) (see MPEP 2144.06).

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

24. No claim is allowed.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

March 29, 2006

Maher Haddad

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600